We interpreted the results of our observational study very conservatively. Some women who used oestrogen developed Alzheimer's disease, but at a significantly later age than that for non-users. In an attempt to determine a dose-response we examined duration of oestrogen use. The median duration of use was 1 year. Women using oestrogen for a year or less had a marginal benefit that was not statistically significant. Women who took oestrogen for longer than a year averaged over 13 years of therapy, and for these women the benefits of oestrogen use seemed most clear.

O'Brien and Liston remind us that oestrogen also has beneficial effects on the cerebral and cardiovascular circulation. It has been suggested,[2] though it remains controversial, that coincident atherosclerosis contributes to the pathogenesis of Alzheimer's disease. We agree that it is possible that oestrogen could modify this effect, but more evidence is required.

Gambassi and colleagues correctly point out that most of the women took unopposed oestrogen. They also state that currently most postmenopausal women with an intact uterus take progesterone in addition to oestrogen to reduce their risk of endometrial cancer. Progesterone and oestrogen act differently on several neurotransmitter systems. However, the work of Goodman et al[3] suggests that the addition of progesterone did not reduce the effects of oestrogen on survival of hippocampal neurons under various models on neurodegeneration.

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Oral rehydration solutions

SIR—When watery diarrhoea begins, how severe it will be or how much fluid will be lost cannot be known. Non-cholera diarrhoea can be nearly as severe as cholera, especially in underserved areas and countries. Gore and colleagues (July 20, p 193)[1] show a slight but non-significant advantage of rice-based oral rehydration solution (ORS) over glucose-based ORS. They acknowledge that in earlier studies when frequent feeding was not given together with ORS there was a clinically important and statistically significant advantage of rice-based ORS;[2] this was most apparent in cholera. When foods containing complex carbohydrates (starches) and protein are given frequently along with ORS this amounts to cereal-based ORS since the food and ORS enter the upper digestive tract simultaneously. Hence, the effect of frequent feeding and rice-based ORS should be and is the same.

In real world situations, as opposed to carefully controlled, well staffed and funded clinical trials, appropriate feedings, and care givers to ensure that they are taken together with glucose-based ORS are often not available. A principal advantage of rice-based ORS is that the salts, water, and cotransporting substrates are always together at low osmolarity even when frequent feeding cannot be accomplished. Clearly, additional feeding, when possible, is highly desirable with all forms of ORS. A second issue is perhaps more serious in cholera and severe diarrhoeas. If sodium in ORS is reduced sufficiently below the 110–130 mmol/L of sodium characteristic of the stools of high output diarrhoea, hyponatraemia will occur. In some cases this could result in water intoxication, convulsions, and death.

One of the main virtues of ORS over the past quarter century has been saving the lives of children with severe watery diarrhoeas—now estimated at more than one million per year globally. It seems ill advised to tamper with success in an attempt to avoid a simple improvement in ORS—ie, substituting rice for glucose—that can improve performance and add an important safety factor in the most severe and deprived settings.

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Oesophageal stricture associated with alendronic acid

SIR—Following the rapid growth in sales of alendronic acid (Fosamax, Merck, Sharp, and Dohme Ltd, Hoddesdon, UK) since its release in the UK in September, 1995, and the concerns raised about oesophageal side-effects,[1] we report a case of oesophageal stricture induced by this drug.

A 47-year-old woman with alcoholic cirrhosis developed osteoporotic vertebral collapse in December, 1995. She was started on disodium etidronate/calcium carbonate cyclical treatment, in addition to regular paracetamol, spironolactone, and frusemide. 3 weeks later the patient read a favourable magazine article about alendronic acid and persuaded her general practitioner to change her treatment.

She was admitted for liver biopsy on July 5, 1996. After discharge she complained of odynophagia and dysphagia to solids. By endoscopy, on July 23, 1996, she could only tolerate a liquid diet. At endoscopy a high inflammatory stricture was encountered at 23 cm. The oesophageal lumen was too narrow to permit passage of the endoscope (Olympus Q230 451, outer diameter of distal tip 10·5 mm). A guide wire was passed and the stricture dilated using the Key-Med Advanced Dilator to 51 French gauge. Subsequent examination revealed no oesophageal pathology immediately distal to the stricture. The squamocolumnar junction was at 35 cm, above a small hiatal hernia, with minimal oesophagitis for 2–3 cm proximal to this.

The high anatomical site of the stricture and the lack of reflux oesophagitis immediately distal to the stricture suggested it was most likely to be drug induced. Of the patient's medication, alendronic acid was the most obvious culprit. On further questioning the patient admitted not taking her tablets in accordance with the package insert. Patients are advised to take alendronic acid with not less than 200 mL plain water, not to lie down for at least 30 min afterwards, and not to take the tablet before going to bed or getting up. Our patient had been waking at 0700 h taking her tablet with a mouthful of water and going back to sleep. Alendronic acid was discontinued and the patient treated with lansoprazole. Her odynophagia and dysphagia resolved

post dilation with this regimen. Repeat endoscopy 1 week later showed no recurrence of the stricture and the endoscope passed easily on this occasion.

Of the 211 oesophageal reactions to alendronic acid reported world wide, 36 were serious. Oesophageal side-effects have been more frequent and more severe than had been anticipated by pre-marketing studies. In about half the reported cases, where relevant information had been recorded, alendronic acid had not been taken in accordance with the prescribing information.[1] Given the severity of this side-effect, the potential dangers of oesophageal dilation, and the fact that many patients taking alendronic acid are likely to be elderly and less mobile, detailed advice on how to take the tablets and a verbal warning about alendronic acid side-effects is required at the time of prescribing.

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1 Committee on Safety of Medicines. *Curr Probl Pharmacovig* 1996; **22:** 5.

Ticlopidine and renal function

SIR—Elsman and Zijlstra's (July 27, p 273)[1] report about deterioration of renal function while on ticlopidine requires comment. Whether ticlopidine worsens renal insufficiency that is already present is doubtful. An atheromatous renal vascular disease is suspected in patients with peripheral artery or coronary artery disease. Patients with pre-existing renal failure are at high risk of nephrotoxicity from contrast media. Depression of glomerular filtration rate usually reaches a nadir a few days after angiography and can be seen until 2 weeks afterwards.[2]

The evolution of plasma creatinine concentration in their patient, which took 15 days to return to baseline, argues against the pathophysiological mechanism Elsman and Zijlstra propose, which is similar to that implicated in renal adverse effects of non-steroidal anti-inflammatory drugs. In this circumstance the improvement of renal function is swift since the mechanism depends on the drug affecting perfusion renal autoregulation; this causes early renal failure, which improves rapidly when perfusion is restored and the drug is discontinued. In fact, deleterious effects of these drugs are more pronounced when systemic perfusion is compromised. Unfortunately, Elsman and Zijlstra do not mention the hydration state of their patient. Further, the mechanism of ticlopidine action is entirely different from other antiplatelet drugs and does not interfere with platelet cyclooxygenase. Rather, it might act by blocking the interaction between fibrinogen and its membrane glycoprotein receptor GPIIb/IIIA,[3] and so cannot be involved in reducing renal perfusion by inhibiting prostaglandin synthesis. Furthermore, the late onset of renal failure (10 days) after introduction of ticlopidine is another argument against the proposed haemodynamic effect of this drug.

If ticlopidine proves a cause of renal failure, one should consider the possibility of a drug-related acute interstitial nephritis.[4] We believe that monitoring renal function and prevention of renal failure by ensuring adequate hydration should be considered in patients with diffuse atheromatous vascular disease when contrast media procedures are planned—particularly in the presence of pre-existing renal insufficiency, with or without ticlopidine treatment.

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Authors' reply

SIR—We agree that atherosclerotic renovascular disease can be present in patients with coronary artery disease and of course we are aware of the possibility of the nephrotoxicity of contrast medium. Contrast medium toxicity, is, however, evident in the first days after the procedure. Our patient had an unchanged plasma creatinine the day after the procedure, with an increase occurring thereafter. This time course of the impairment of renal function is not compatible with a reaction to contrast medium. The hydration state of our patient was normal; he did not use a diuretic drug, had no restriction in fluid intake, and was on a normal diet. The effect of ticlopidine on platelet function may indeed be different from other antiplatelet drugs, but that does not mean that its effects on renal function are not analogous to the side-effects of non-steroidal anti-inflammatory drugs. It takes several days before the effect of ticlopidine is maximum, which therefore fits very well with the time-course of the impairment in renal function in our patient. We considered the possibility of drug-related acute interstitial nephritis but our patient lacked the other diagnostic clues for that diagnosis.

We perform over 4000 diagnostic and therapeutic cardiac catheterisations every year. Adequate hydration and monitoring of renal function, especially in patients with diffuse atherosclerotic disease, are routine daily practice. Nevertheless, the fact remains that one of our patients who started ticlopidine after such a procedure did develop a gradual impairment of renal function that returned to the baseline situation without any other change in the therapeutic regimen apart from stopping ticlopidine.

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SIR—Elsman and Zijlstra[1] report reversible impairment of renal function associated with the potent antiplatelet agent ticlopidine. This effect was first reported in a woman who had been given the drug as prophylaxis against transient cerebral ischaemic attacks.[2] The renal pathology in this case, confirmed through biopsy, was an acute interstitial nephritis. Ticlopidine was discontinued and corticosteroids were given. She needed haemodialysis for about 2 weeks before her urea and creatinine values returned to normal. We report another case of disturbed renal function linked to ticlopidine.

A 49-year-old man presented at our institution with unstable angina after acute myocardial infarction. He underwent coronary angiography, with subsequent percutaneous transluminal coronary angioplasty and primary stent implantation to an isolated lesion of the left anterior descending coronary artery. After excellent angiographical and clinical assessments, he was discharged on an antithrombotic regimen of ticlopidine and aspirin, with instructions for routine haematological monitoring. He returned to the ward 6 days after discharge because of a generalised urticarial rash, and fever. His serum creatinine had increased from a baseline post-procedural value of 97 µmol/L to 169 µmol/L at his re-presentation. Ticlopidine was stopped, but over the next 3 days there was further